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# Efficient Asymmetric Synthesis of Quaternary (*E*)-Vinylglycines by Deconjugative Alkylation of Dehydroamino Acids

**Matthew C. Jones, Stephen P. Marsden,* and Dulce M. Muñoz Subtil**

*School of Chemistry, University of Leeds, Leeds LS2 9JT, U.K.*

*s.p.marsden@leeds.ac.uk*

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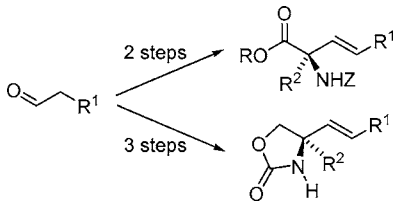
## ABSTRACT




**A two-step protocol for the asymmetric synthesis of protected quaternary (*E*)-vinylglycines from simple aldehydes is reported. The key step is a regiocontrolled deconjugative asymmetric alkylation of dehydroamino acids, giving the targets as single geometric isomers with high diastereoselectivity (92–96% de). The products can be converted to valuable quaternary *β*-amino alcohols by chemoselective reduction.**

Quaternary amino acids bearing adjacent hydroxyl functionalities occur in a wide variety of important biologically active natural products such as the immunosuppressant myriocin **1**,[1] the proteasome inhibitor lactacystin **2**,[2] and the cytotoxic neooxazolomycin **3**[3] (Figure 1). In the context of complex synthetic targets such as these, the challenges associated with the construction of quaternary asymmetric centers are exacerbated by the presence of the neighboring stereogenic centers and polar functionality, and there is considerable scope for improved methods for the preparation of these functional groups.[4]

We reasoned that protected quaternary (*E*)-vinylglycines[5] such as **4** would be useful chiral building blocks in this

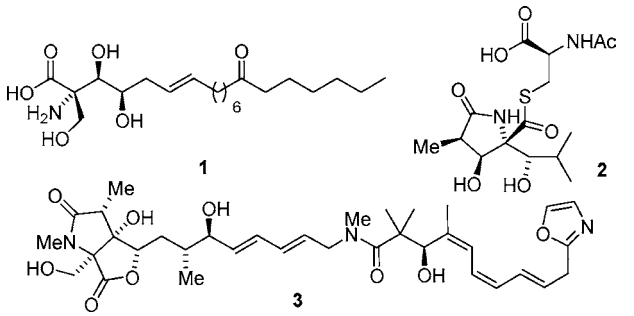



**Figure 1.** Representative polyhydroxy quaternary amino acids.

context because diastereoselective functionalization of the olefin would allow access to the substituted side chains present in the natural product targets. We recently reported

(1) Kluepfel, D.; Bagli, J.; Baker, H.; Charest, M. P.; Kudelski, A.; Sehgal, S. N.; Vezina, C. *J. Antibiot.* **1972**, *25*, 109−115.
(2) (a) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113−116. (b) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117−118.
(3) Takahashi, K.; Kawabata, M.; Uemura, D.; Iwadare, S.; Mitomo, R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett.* **1985**, *26*, 1077−1078.
(4) For reviews of synthetic approaches to quaternary amino acids, see: (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517−3599. (b) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127−5143. (c) Kang, S. H.; Kang, S. Y.; Lee, H.-S.; Buglass, A. J. *Chem. Rev.* **2005**, *105*, 4537−4558.

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that readily available *N*-(benzyloxycarbonyl)-protected dehydroamino acids (**5**, R = Me) undergo efficient double deprotonation with lithium amide bases in the presence of lithium chloride and that the resulting dienolates **6** undergo exclusive α-protonation to generate substituted (*E*)-vinylglycines (**4**, $R^2$ = H) with perfect control of olefin geometry.[6−8] The potential extension of this method to the asymmetric synthesis of quaternary (*E*)-vinylglycines would rest upon (a) the alkylation reactions showing a similarly high preference for reaction at the α-position and (b) the identification of a suitable chiral auxiliary to control absolute stereochemistry in the alkylation (Figure 2).

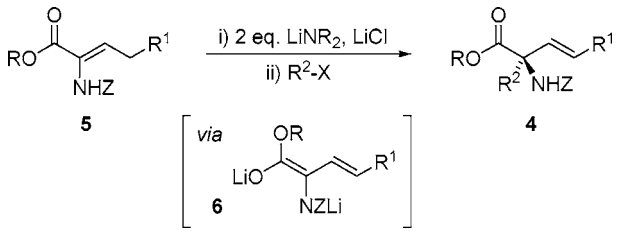
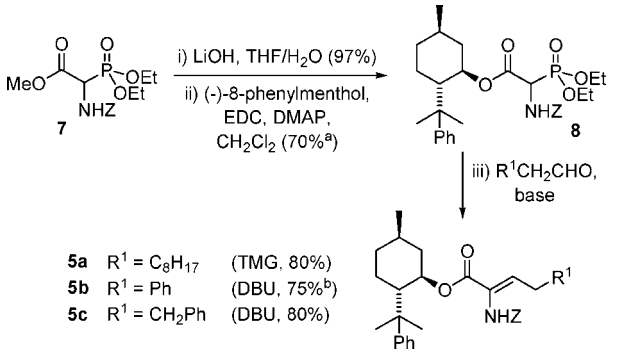



**Figure 2.** Deconjugative alkylation of dehydroamino acids **5** as a route to quaternary (*E*)-vinylglycines **4**.

Seebach has previously reported the asymmetric alkylation of dehydroamino acids based upon dihydroimidazolone templates, but these chiral templates are expensive and nonrecyclable.[9] Berkowitz has elegantly demonstrated that the dianions of chiral *N*-benzoyl dehydrohomoalanine esters undergo stereoselective alkylation leading to a range of simple α-vinyl amino acids.[10] However, in this chemistry, the α- vs γ-regioselectivity of the alkylation reaction is greatly dependent on the nature of the electrophile, and the synthesis of the dehydrohomoalanine precursor (five steps from *N*-benzoyl homoserine lactone) is not amenable to the synthesis of higher homologues. We report here that dienolates derived from chiral *Z*-protected dehydroamino acids **5** (R = 8-phenylmenthyl), prepared in one step from simple aldehydes, undergo regiocontrolled α-alkylation, yielding quaternary (*E*)-vinylglycines **4** with perfect control of olefin geometry and high diastereoselectivity.

At the outset, we sought a short and general approach to substrates **5** to maximize the efficiency and scope of the overall sequence and targeted phosphonate **8** as our key stock building block. Saponification of readily available[11] phosphonoglycine ester **7** was followed by EDC-mediated coupling of the resulting acid with (−)-8-phenylmenthol to give **8** in 68% yield over two steps (Scheme 1). The synthesis was

**Scheme 1.** Concise Synthesis of Chiral Dehydramino Acids **5a−c**




[a] 89% based on recovered 8-phenylmenthol. [b] Isolated as a 7:3 mixture of **5b** and its deconjugated styrylglycine isomer.

readily amenable to scale-up (>25 g prepared in a single run). Phosphonate **8** underwent smooth Horner−Wadsworth−Emmons coupling with decanal, phenylacetaldehyde, and 3-phenylpropanal to furnish the dehydroamino acids **5a−c**, respectively, in 75−80% yield.

We then turned our attention to the alkylation of these substrates. After a brief period of optimization, we found that dienolate formation under conditions similar to those identified in our earlier deconjugation studies[6,8a] (3 equiv of lithium diisopropylamide in the presence of 6 equiv of lithium chloride) followed by exposure to an excess of electrophile gave reproducibly good to excellent yields of the alkylated products. We then examined the scope of the reaction in terms of both nucleophile and electrophile, and the results are presented in Table 1.

Pleasingly, the reaction tolerates the presence of a range of side chains in the nucleophile, generating alkyl-, phenyl-, and benzyl-substituted alkenes from substrates **5a−c**, respectively. In all cases, the sole observable product was that

(5) Other synthetic approaches to quaternary (*E*)-vinylglycines include: (a) sigmatropic rearrangement: Armstrong, A.; Challinor, L.; Cooke, R. S.; Moir, J. H.; Treweeke, N. R. *J. Org. Chem.* **2006**, *71*, 4028−4030. Shangde, J.; Liebscher, J. *Z. Naturforsch. B: Chem. Sci.* **2002**, *57*, 377−382. (b) Addition of alkenylzirconocenes to a α-imino esters: Wipf, P.; Stephenson, C. R. J. *Org. Lett.* **2003**, *5*, 2449−2452. (c) Strecker reaction: Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634−5635. (d) Self-regeneration of stereocenters approach from vinylglycine: Berkowitz, D. B.; Chisowa, E.; McFadden, J. M. *Tetrahedron* **2001**, *57*, 6329−6343. Berkowitz, D. B.; McFadden, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 11031−11032. (e) Vinylation of alanine enolates: Ma, D.; Ma, Z.; Jian, J.; Yang, Z.; Zheng, C. *Tetrahedron: Asymmetry* **1997**, *8*, 889−893. Pajouhesh, H.; Curry, K.; Pajouhesh, H.; Meresht, M. H.; Patrick, B. *Tetrahedron: Asymmetry* **2003**, *14*, 593−596. (f) Alkylation of styrylglycine enolates: Chang, C.-J.; Fang, J.-M.; Lee, G.-H.; Wang, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3587−3593. See also ref 9.

(6) Alexander, P. A.; Marsden, S. P.; Muñoz-Subtil, D. M.; Reader, J. C. *Org. Lett.* **2005**, *7*, 5433−5436.

(7) For related studies, see: (a) Hoppe, I.; Schöllkopf, U. *Synthesis* **1982**, 129−131. (b) Daumas, M.; Vo Quang, L.; Vo Quang, Y.; Le Goffic, F. *Tetrahedron Lett.* **1989**, *30*, 5121−5124.

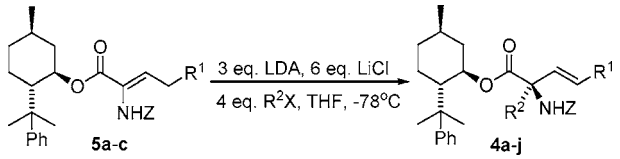
(8) For alkylations of dienediolates leading to quaternary α-hydroxy acids, see: (a) Newton, R.; Marsden, S. P. *Synthesis* **2005**, 3263−3270. (b) Koft, E. R.; Williams, M. D. *Tetrahedron Lett.* **1986**, *27*, 2227−2230.

(9) Seebach, D.; Buerger, H. M.; Schickli, C. P. *Liebigs Ann. Chem.* **1991**, 669−684. See also: Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C. P.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237−261. Weber, T.; Aeschimann, R.; Maetzke, T.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1365−1377.

(10) Berkowitz, D. B.; McFadden, J. M.; Sloss, M. K. *J. Org. Chem.* **2000**, *65*, 2907−2918.

(11) (a) Shankar, R.; Scott, A. I. *Tetrahedron Lett.* **1993**, *34*, 231−234. (b) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53−60. Additionally, the trimethyl phosphonoglycinate derivative is commercially available (Aldrich).

**Table 1.** Diastereoselective Deconjugative Alkylation of Dehydroamino Acids **5**




| entry | $R^1$ | $R^2X$ | product | yield[a] | dr (de)[b] |
|---|---|---|---|---|---|
| 1 | $C_8H_{17}$ | MeI | **4a** | 91% | >95:5 (95) |
| 2 | $C_8H_{17}$ | EtI[c] | **4b** | 97% | >95:5 (94) |
| 3 | $C_8H_{17}$ | BnI | **4c** | 60% | >95:5 (96) |
| 4 | $C_8H_{17}$ | allyl I | **4d** | 84% | >95:5 (93) |
| 5 | $C_8H_{17}$ | BOMCl[d] | **4e** | 35% | >95:5 (93) |
| 6 | $C_8H_{17}$ | $ECH_2Cl$[e] | **4f** | 90% | >95:5 (95) |
| 7 | Ph | MeI | **4g** | 82% | 97:3 (93) |
| 8 | Ph | BOMCl[d] | **4h** | 44% | >95:5 (95) |
| 9 | Bn | MeI | **4i** | 90% | >95:5 (95) |
| 10 | Bn | BOMCl[d] | **4j** | 49% | >95:5 (92) |

[a] Isolated yield. [b] dr determined by inspection of 500 MHz $^1$H NMR spectra. The value in parenthesis is the accurate de inferred by the ee of oxazolidones **12** (see Table 2). [c] 20 equiv of electrophile was used. [d] The additive used was lithium iodide. [e] E = $^t$BuO$_2$C.

arising from regioselective α-alkylation, regardless of the electrophile used. With benzylic and allylic electrophiles, the use of iodide as the leaving group was found to be essential to achieve high yields (entries 3 and 4); the use of bromides and chlorides gave poor conversions and led to products arising from benzylic/allylic carbenoid formation. Protected hydroxymethyl side chains were successfully installed using benzyloxymethyl chloride, but these reactions benefitted from the substitution of the lithium chloride additive by lithium iodide (entries 5, 8, and 10): presumably, an in situ Finkelstein displacement generates the more reactive benzyloxymethyl iodide as the active electrophile. The use of ethyl bromo- or chloroacetate gave unexpectedly poor diastereoselectivity in the alkylation (ca. 75:25 in both cases); this was easily overcome by the use of *tert*-butyl chloroacetate as the electrophile (entry 6).

In terms of stereochemistry, as observed in our previous studies,[6,8a] the products were all formed as single geometric alkene isomers with (*E*)-stereochemistry, an outcome that was rationalized on the basis of minimization of $A_{1,3}$-strain in an acyclic transition state for deprotonation. In all cases bar one (entry 7), only a single stereoisomer could be detected by $^1$H and $^{13}$C NMR, leading to the tentative assignment of diastereoselectivity at a level of >95:5. Pleasingly, the high degree of stereocontrol in all cases was subsequently verified and unambiguously quantified by reductive cleavage of the phenylmenthol auxiliary to yield oxazolidinones **12** (vide infra) which were characterized by chiral HPLC comparison with genuine racemic samples. The sense of asymmetric induction at the newly formed center was inferred from previous studies on the alkylation of phenylmenthyl glycinyl esters[10,12] and was proven unambiguously in one case by X-ray crystallographic studies of a derivative.[13]

Having achieved a highly efficient two-step synthesis of chiral quaternary (*E*)-vinylglycines from simple aldehydes, we next turned our attention to the synthetic manipulation of these entities. Quaternary β-amino alcohols are also key substructures of a wide range of natural products, such as the manzacidins **9**[14] and the antiviral virantmycin **10**,[15] as well as of pharmaceuticals such as the selective 5-HT uptake inhibitor cericlamine **11** (Figure 3).

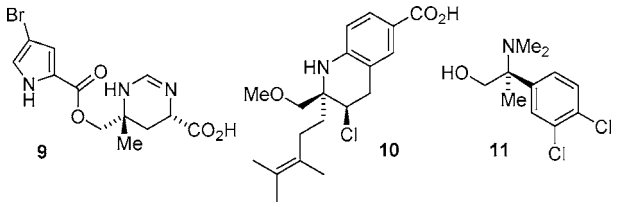



**Figure 3.** Representative quaternary β-amino alcohol containing targets.

We found that chemoselective reductive cleavage of the phenylmenthyl esters **4** could be achieved in a two-step, one-pot operation. Exposure to lithium aluminum hydride at 0 °C resulted in the partial reduction of the ester to the corresponding aldehyde; further reduction was effected by treatment with basic methanolic sodium borohydride, which proceeded with concomitant ring closure to yield oxazolidinones **12** (Table 2). The use of low temperatures in the lithium aluminum hydride reduction was crucial because reaction at elevated temperatures caused competitive reduction of the carbamate function. As an alternative protocol, the use of excess lithium borohydride effected selective reduction of the ester directly to the primary alcohol, which underwent partial cyclization to **12** in situ; this process could be forced to completion by addition of sodium hydroxide, giving good yields of **12** in a one-pot operation (entry 3). The ee of these compounds was verified by chiral HPLC comparison with racemic samples. In the case of amino acid **4f**, the carboxymethyl side chain also undergoes reduction to a primary alcohol (entry 6); competitive nucleophilic ring closure then leads to a separable mixture of the oxazolidinone **12f** and the corresponding oxazinan-2-one (combined 84% yield), both of 95% ee.

Finally, we wished to demonstrate that our alkylated products could be smoothly converted to the free amino acids. Despite potential concerns regarding the highly hindered nature of these substrates, the use of relatively mild modified Gassman conditions[10,16] led to cleavage of both the

(12) (a) McIntosh, J. M.; Thangarasa, R.; Foley, N. K.; Ager, D. J.; Froen, D. E.; Klix, R. C. *Tetrahedron* **1994**, *50*, 1967−1974. (b) Berkowitz, D. B.; Smith, M. K. *J. Org. Chem.* **1995**, *60*, 1233−1238.

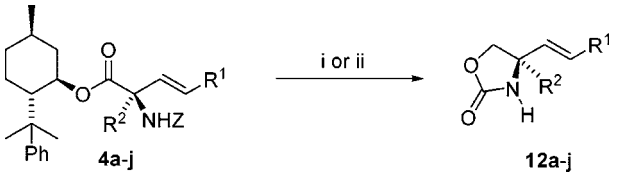
(13) See Supporting Information for details.

(14) Kobayashi, J.; Kanda, F.; Ishibashi, M.; Shigemori, H. *J. Org. Chem.* **1991**, *56*, 4574−4576.

(15) (a) Omura, S.; Nakagawa, A.; Hashimoto, H.; Oiwa, R.; Iwai, Y.; Hirano, A.; Shibukawa, N.; Kojima, Y. *J. Antibiot.* **1980**, *33*, 1395−1396. (b) Omura, S.; Nakagawa, A. *Tetrahedron Lett.* **1981**, *22*, 2199−2202.

(16) Gassman, P. G.; Schenk, W. N. *J. Org. Chem.* **1977**, *42*, 918−920.

**Table 2.** Chemoselective Reductive Cyclization of Quaternary (*E*)-Vinylglycines **4** to Oxazolidinones **12**



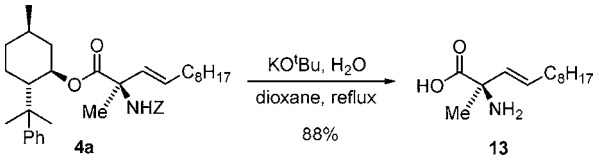

| entry | method[a] | product | $R^1$ | $R^2$ | yield[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | i | **12a** | $C_8H_{17}$ | Me | 33 | 95 |
| 2 | i | **12b** | $C_8H_{17}$ | Et | 42 | 94 |
| 3 | ii | **12c** | $C_8H_{17}$ | Bn | 85 | 96 |
| 4 | i | **12d** | $C_8H_{17}$ | allyl | 42 | 93 |
| 5 | i | **12e** | $C_8H_{17}$ | BOM | 35 | 93 |
| 6 | ii[d] | **12f** | $C_8H_{17}$ | $(CH_2)_2OH$ | 64[e] | 95 |
| 7 | i | **12g** | Ph | Me | 60 | 93 |
| 8 | i | **12h** | Ph | BOM | 73 | 95 |
| 9 | i | **12i** | Bn | Me | 56 | 95 |
| 10 | i | **12j** | Bn | BOM | 50 | 92 |

[a] Method i: 4 equiv of $LiAlH_4$, THF, 0 °C, then MeOH, $NaBH_4$, 1 M NaOH. Method ii: 16 equiv of $LiBH_4$, $Et_2O$, reflux, then 1 M NaOH, THF. [b] Isolated yield. [c] Determined by chiral HPLC analysis in comparison with racemic samples. [d] 32 equiv of $LiBH_4$ used. [e] 20% of the regioisomeric oxazinan-2-one (95% ee) was also formed.

ester and carbamate functions of **4a**, yielding the free amino acid **13** in unoptimized 88% yield, with an 82% recovery of the (−)-8-phenylmenthol auxiliary (Scheme 2).

In summary, we have developed a novel asymmetric synthesis of protected quaternary (*E*)-vinylglycines **4** in just two steps from simple aldehydes and the newly introduced, readily prepared phosphonate **8**. The key step is a highly regio-, stereo-, and diastereoselective deconjugative alkylation reaction of dehydroamino acids **5**. These products (**4**) can be conveniently manipulated to the free amino acid **13** or protected amino alcohols **12**. Both the amino acids and the amino alcohols are expected to find significant application in target synthesis, and the results of our own studies in this area will be reported in due course.

**Scheme 2.** Deprotection to Free Quaternary Vinylglycine

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**Supporting Information Available:** Experimental protocols and spectroscopic data for compounds **4**, **5**, **8**, **12**, and **13** plus copies of $^1H$ and $^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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